pg*hr/ml; and 2) a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estrone of about 43 pg*hr/ml to about 65 pg*hr/ml.

In some embodiments, a pessary provided herein comprises about 25 µg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C$_{max}$) of estrone sulfate of about 416 pg*hr/ml to about 613 pg*hr/ml; and 2) a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estrone sulfate of about 3598 pg*hr/ml to about 5291 pg*hr/ml.

In some embodiments, a pessary provided herein comprises about 10 µg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C$_{max}$) of estradiol of about 12 pg*hr/ml to about 18 pg*hr/ml; and 2) a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estradiol of about 42 pg*hr/ml to about 63 pg*hr/ml. In some embodiments, the pessary further provides a corrected geometric mean time to peak plasma concentration (T$_{max}$) of estradiol of about 1 hrs to about 3 hrs.

In some embodiments, a pessary provided herein comprises about 10 µg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C$_{max}$) of estrone of about 4 pg*hr/ml to about 7 pg*hr/ml; and 2) a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estrone of about 20 pg*hr/ml to about 31 pg*hr/ml. In some embodiments, the pessary further provides a corrected geometric mean time to peak plasma concentration (T$_{max}$) of estrone of about 4 hrs to about 8 hrs.

In some embodiments, a pessary provided herein comprises about 10 µg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C$_{max}$) of estrone sulfate of about 10 pg*hr/ml to about 16 pg*hr/ml; and 2) a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estrone sulfate of about 56 pg*hr/ml to about 84 pg*hr/ml. In some embodiments, the pessary further provides a corrected geometric mean time to peak plasma concentration (T$_{max}$) of estrone sulfate of about 4 hrs to about 7 hrs.

In some embodiments, a pessary provided herein comprises about 4 µg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C$_{max}$) of estradiol of about 4 pg*hr/ml to about 8 pg*hr/ml; and 2) a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estradiol of about 16 pg*hr/ml to about 26 pg*hr/ml. In some embodiments, the pessary further provides a corrected geometric mean time to peak plasma concentration (T$_{max}$) of estradiol of about 0.25 hrs to about 2 hrs.

In some embodiments, a pessary provided herein comprises about 4 µg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C$_{max}$) of estrone of about 1 pg*hr/ml to about 3 pg*hr/ml; and 2) a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estrone of about 8 pg*hr/ml to about 13 pg*hr/ml. In some embodiments, the pessary further provides a corrected geometric mean time to peak plasma concentration (T$_{max}$) of estrone of about 1 hrs to about 4 hrs.

In some embodiments, a pessary provided herein comprises about 4 µg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C$_{max}$) of estrone sulfate of about 4 pg*hr/ml to about

7 pg*hr/ml; and 2) a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estrone sulfate of about 22 pg*hr/ml to about 34 pg*hr/ml. In some embodiments, the pessary further provides a corrected geometric mean time to peak plasma concentration (T$_{max}$) of estrone sulfate of about 1 hrs to about 3 hrs.

Also provided herein is a pessary comprising about 1 µg to about 25 µg of estradiol, wherein administration of the pessary to a patient provides a corrected geometric mean peak plasma concentration (C$_{max}$) of estradiol that is less than about 30 pg*hr/ml. For example, administration of the pessary to a patient provides a corrected geometric mean peak plasma concentration (C$_{max}$) of estradiol that is less than about 18 pg*hr/ml.

In some embodiments, a pessary comprising about 1 µg to about 25 µg of estradiol is provided, wherein administration of the pessary to a patient provides a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estradiol that is less than about 112 pg*hr/ml. For example, administration of the pessary to a patient provides a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estradiol that is less than about 63 pg*hr/ml.

In some embodiments, a pessary comprising about 1 µg to about 25 µg of estradiol is provided, wherein administration of the pessary to a patient provides a corrected geometric mean peak plasma concentration (C$_{max}$) of estrone that is less than about 14 pg*hr/ml. For example, administration of the pessary to a patient provides a corrected geometric mean peak plasma concentration (C$_{max}$) of estrone that is less than about 7 pg*hr/ml.

In some embodiments, a pessary comprising about 1 µg to about 25 µg of estradiol is provided, wherein administration of the pessary to a patient provides a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estrone that is less than about 65 pg*hr/ml. For example, administration of the pessary to a patient provides a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estrone that is less than about 31 pg*hr/ml.

In some embodiments, a pessary comprising about 1 µg to about 25 µg of estradiol is provided, wherein administration of the pessary to a patient provides a corrected geometric mean peak plasma concentration (C$_{max}$) of estrone sulfate that is less than about 613 pg*hr/ml. For example, administration of the pessary to a patient provides a corrected geometric mean peak plasma concentration (C$_{max}$) of estrone sulfate that is less than about 16 pg*hr/ml.

In some embodiments, a pessary comprising about 1 µg to about 25 µg of estradiol is provided, wherein administration of the pessary to a patient provides a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estrone sulfate that is less than about 5291 pg*hr/ml. For example, administration of the pessary to a patient provides a corrected geometric mean area under the curve (AUC)$_{0-24}$ of estrone sulfate that is less than about 84 pg*hr/ml.

Further provided herein is a pessary comprising about 1 µg to about 25 µg of estradiol, wherein administration of the pessary to the proximal region of the vagina of a patient provides a therapeutically effective concentration of estradiol over 24 hours in the proximal region of the vagina.

This disclosure also provides a method of treating an estrogen-deficient state, the method comprising administering to a patient in need thereof, a pessary as provided herein. In some embodiments, a method of treating vulvovaginal atrophy is provided, the method comprising administering to a patient in need thereof, a pessary as provided herein.

In some embodiments of the methods provided herein, treatment comprises reducing the severity of one or more